PATENT COOPERATION TREATY

PCT

14

REC'D 05 JUL 2001
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SD/FB/BC45226		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/02478	20/03/2000	26/03/1999
International Patent Classification (IPC) or national classification and IPC C12N15/11		
Applicant SMITHKLINE BEECHAM BIOLOGICALS S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25/09/2000	03.07.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer SCHEFFZYK, I Telephone No. +49 89 2399 8602

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/02478

I. Basis f th r p rt

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-45 as originally filed

Claims, No.:

1-38 as received on 23/03/2001 with letter of 21/03/2001

Drawings, sheets:

1/2,2/2 as originally filed

Sequence listing part of the description, pages:

1-14, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 15,25,26,29-32,34-38.

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☒ the claims, or said claims Nos. 15, 25,26,29-32,34-38 are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. R asoned statement under Articl 35(2) with regard to novelty, inventiv step or industrial applicability; citations and explanati ns supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4,9-12,20-24
	No:	Claims	5-8, 13, 14, 16-19, 27, 28, 33
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14,16-24,27,28,33
Industrial applicability (IA)	Yes:	Claims	1-14,16-24, 27, 28, 33
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

SECTION V----------

Applicant's comments have been carefully taken into account but are not deemed suitable to establish novelty and inventive step of presently claimed subject-matter:

SEQ.ID. NO. 51 described in WO 99/06548 (1) is identical to SEQ.ID.NO. 2 in the first 98 amino acid residues. Since at present it cannot be ruled out that the sequence taught in (1) also has the immunogenic properties as required in claim 5 said sequence is deemed novelty destroying for claim 5. Correspondingly, the subject-matter of claims 6-8, 13(c), 14, 16-19, 23 and 28-32 also is anticipated by the teaching of (1).
In addition, the same applies correspondingly for the EST sequences taught in EMBL Database Accession Number AA890726 (2) and EMBL Database Accession Number AI301140 (3) which have high similarity (98.7% and 100%, respectively) with the reverse strand of presently claimed SEQ.ID.NOS. 1 and 3 over a given region (nt. 3265-2736 and nt. 3255- 2692, respectively). Thus, (2) and (3) also destroy novelty of claim 8, 13(c), 17 and 33.
Claim 27 lacks novelty since any readily available compound may be covered by the scope of said claim. Correspondingly, claim 28(a) also lacks novelty.
To sum up: claims 5-8, 13, 14, 16-19, 27,28 and 33 do not meet the requirements of Art. 33(2)(3) PCT.

Concerning the remaining claims which are deemed novel in the light of the available prior art the presence of an inventive step cannot be acknowledged for the following reasons:
In the absence of any **facts and data** concerning the function of presently claimed sequences the problem underlying present application only can be seen in the mere provision of a further nucleic acid sequence encoding any polypeptide. With respect to this it is noted that the application as filed either only repeats the wording of the claims (which is not a support in the sense of Guidelines C-III 6.3 PCT) or only contains vague statements or speculations concerning the possible function

thereof which, however, also cannot be considered as a technical support in the meaning of Art. 6 PCT and Guideline C-III 6.3 PCT. However, the provision of any sequence by using routine methods lacks inventive activity. Therefore, claims 1-4, 9-12, 20-24 do not comply with the requirements of Art. 33(3) PCT.

SECTION VI----------

WO 99/54461

EMBL Database Accession Number AI672868 (19.05.99)

EMBL Database Accession Number ABO37745 (14.03.00)

SECTION VII----------

1). The sequence of the claims should be rearranged: claim 33 should follow claim 13 and claim 34 should follow claim 18.

2). With respect to the term "incorporated by reference" Applicant's attention is drawn to Guidelines C-II 4.4 and C-II 4.17 PCT.

3). For the subject-matter of claim 15 no basis can be found in the application as originally filed. Correspondingly, said claim does not comply with the requirements of Art. 34(2)(b) PCT. The same applies correspondingly to claim 34 containing a reference to claim 15.

SECTION VIII----------

1). The expressions "larger" and "similar" are subjective terms and thus open to interpretation. Correspondingly, the use thereof renders the scope of claims containing at least one of said expression unclear.

2). Claim 24 is objected to under Art. 5 and 6 PCT since the function of

CASB619 is not mentioned in the application as filed. Thus, a person skilled in the art trying to carry out the method according to claim 23 actually does not know what kind of function(s) should be altered.

3). In addition, taking into account that the immunogenic properties of the polypeptide encoded by SEQ.ID.NO.2 are not specified in the specification the definition of the claimed fragments used in claims 5 and 13(c) is not deemed appropriate since it is unclear to a skilled person which fragments are covered by the scope of said claims and which are not.

4). Claims 27, 28(a) and (c) are completely speculative. The application as filed does not give any example which would meet the requirements set out in these claims.

5). Claims relating to the use of the claimed protein/polynucleotides for medical treatments are not technically supported by the specification.

6). In addition, in so far as present application does not contain any information concerning the function of the claimed polypeptides industrial applicability of claims directed to polypeptides is not met (Art. 33(4) PCT).

Claims

1. An isolated polypeptide comprising an amino acid sequence which has at least 70% identity to the amino acid sequence of SEQ ID NO:2 over the entire length of of SEQ ID NO:2.

2. An isolated polypeptide as claimed in claim 1 in which the amino acid sequence has at least 95% identity to SEQ ID NO:2.

3. The polypeptide as claimed in claim 1 comprising the amino acid sequence of SEQ ID NO:2.

4. The isolated polypeptide of SEQ ID NO:2.

5. A polypeptide comprising an immunogenic fragment of a polypeptide as claimed in any one of claims 1 to 4 in which the immunogenic activity of the immunogenic fragment is substantially the same as the polypeptide of SEQ ID NO:2

6. A polypeptide as claimed in any of claims 1 to 5 wherein said polypeptide is part of a larger fusion protein.

7. A polypeptide as claimed in any of claims 1 to 6 chemically conjugated to a carrier protein.

8. An isolated polynucleotide encoding a polypeptide as claimed in any of claims 1 to 6.

9. An isolated polynucleotide comprising a nucleotide sequence encoding a polypeptide that has at least 70% identity to the amino acid sequence of SEQ ID NO:2, over the entire length of SEQ ID NO:2; or a nucleotide sequence complementary to said isolated polynucleotide.

10. An isolated polynucleotide comprising a nucleotide sequence that has at least 70% identity to a nucleotide sequence encoding a polypeptide of SEQ ID NO:2, over the entire coding region; or a nucleotide sequence complementary to said isolated polynucleotide.

11. An isolated polynucleotide which comprises a nucleotide sequence which has at least 70% identity to that of SEQ ID NO:1 over the entire length of SEQ ID NO:1; or a nucleotide sequence complementary to said isolated polynucleotide.

12. The isolated polynucleotide as defined in any one of claims 8 to 11 in which the identity is at least 95%.

13. An isolated polynucleotide selected from:

(a) a polynucleotide comprising a nucleotide sequence encoding the polypeptide of SEQ ID NO:2;

(b) the polynucleotide of SEQ ID NO:1; and

(c) a polynucleotide obtainable by screening an appropriate library under stringent hybridization conditions with a labeled probe having the sequence of SEQ ID NO:1 or a fragment thereof said polynucleotide encoding a protein which has similar immunogenic properties to those of the protein of sequence ID NO:2

or a nucleotide sequence complementary to said isolated polynucleotide

14. An expression vector or a recombinant live microorganism comprising an isolated polynucleotide according to any one of claims 8 - 13.

15. A host cell comprising the expression vector of claim 14 or the isolated polynucleotide of claims 8 to 13.

16. A process for producing a polypeptide of claims 1 to 7 comprising culturing a host cell of claim 15 under conditions sufficient for the production of said polypeptide and recovering the polypeptide from the culture medium.

17. A vaccine comprising an effective amount of the polypeptide of any one of claims 1 to 7 and a pharmaceutically acceptable carrier.

18. A vaccine comprising an effective amount of the polynucleotide of any one of claims 8 to 13 and a pharmaceutically effective carrier.

19. A vaccine comprising an effective amount of antigen presenting cells, modified by in vitro loading with a polypeptide of any one of claims 1 to 7, or genetically modified in vitro to express a polypeptide of claims 1 to 7 and a pharmaceutically effective carrier.

20. A vaccine as claimed in any one of claims 17 to 19 which additionally comprises a TH-1 inducing adjuvant.

21. A vaccine as claimed in claim 20 in which the TH-1 inducing adjuvant is selected from the group of adjuvants comprising: 3D-MPL, QS21, a mixture of QS21 and cholesterol, and a CpG oligonucleotide.

22. An antibody immunospecific for the polypeptide or immunological fragment as claimed in any one of claims 1 to 5.

23. A method for screening to identify compounds which stimulate or which inhibit the function of the polypeptide of any one of claims 1 to 5 which comprises a method selected from the group consisting of:

(a) measuring the binding of a candidate compound to the said polypeptide (or to the cells or membranes bearing the polypeptide) or a fusion protein thereof by means of a label directly or indirectly associated with the candidate compound;

(b) measuring the binding of a candidate compound to the said polypeptide (or to the cells or membranes bearing the polypeptide) or a fusion protein thereof in the presence of a labeled competitior;

(c) testing whether the candidate compound results in a signal generated by activation or inhibition of the said polypeptide, using detection systems appropriate to the cells or cell membranes bearing the polypeptide;

(d) mixing a candidate compound with a solution containing a polypeptide of any one of claims 1 to 7, to form a mixture, measuring activity of the polypeptide in the mixture, and comparing the activity of the mixture to a standard; or

(e) detecting the effect of a candidate compound on the production of mRNA encoding said polypeptide and said polypeptide in cells, using for instance, an ELISA assay.

24. A method for the treatment of a subject by immunoprophylaxis or therapy comprising *in vitro* induction of immune responses to a molecule of any one of claims 1 to 5, using *in vitro* incubation of the polypeptide of any one of claims 1 to 7 or the polynucleotide of any one of claims 8 to 13 with cells from the immune system of a mammal, and reinfusing these activated immune cells to the mammal for the treatment of disease.

25. A method as claimed in claim 24 wherein the treatment is for ovarian or colon cancer.

26. An agonist or antagonist to the polypeptide of claims 1 to 5.

27. A compound which is:
(a) an agonist or antagonist to the polypeptide of claims 1 to 5;
(b) isolated polynucleotide of claims 8 to 13; or
(c) a nucleic acid molecule that modulates the expression of the nucleotide sequence encoding the polypeptide of any one of claims 1 to 5;
for use in therapy.

28. A process for diagnosing a disease or a susceptibility to a disease in a subject related to expression or activity of a polypeptide of any one of claims 1 to 5 in a subject comprising analyzing for the presence or amount of said polypeptide in a sample derived from said subject.

29. A process for diagnosing a disease or a susceptibility to a disease in a subject related to expression or activity of a polynucleotide of any one of claims 8 to 13 in a subject comprising analyzing for the presence or amount of said polynucleotide in a sample derived from said subject.

30. A process for diagnosing the presence of colon cancer or a susceptibility to colon cancer in a subject related to expression or activity of a polypeptide of any one of claims 1 to 5 in a subject comprising analyzing for the presence or amount of said polypeptide in a sample derived from said subject.

31. A process for diagnosing the presence of colon cancer or a susceptibility to colon cancer in a subject related to expression or activity of a polynucleotide of any one of claims 8 to 13 in a subject comprising analyzing for the presence or amount of said polynucleotide in a sample derived from said subject.

32. An isolated polynucleotide selected from the group consisting of:
(a) an isolated polynucleotide comprising a nucleotide sequence which has at least 70% identity to SEQ ID NO:3 over the entire length of SEQ ID NO:3;
(b) an isolated polynucleotide comprising the polynucleotide of SEQ ID NO:3;
(c) the polynucleotide of SEQ ID NO:3.

33. A live vaccine composition comprising an expression vector or recombinant live micro-organism according to claim 14.

34. Use of a polynucleotide as claimed in any one of claims 8 to 13 for the manufacture of a medicament in the treatment of carcinoma.

35. Use of a polynucleotide as claimed in any one of claims 8 to 13 for the manufacture of a medicament in the treatment of colon carcinoma.

36. Use of a polypeptide as claimed in any one of claims 1 to 7 for the manufacture of a medicament in the treatment of carcinoma.

37. Use of a polypeptide as claimed in any one of claims 1 to 7 for the manufacture of a medicament in the treatment of colon carcinoma.